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Eye movements in essential tremor patients with parkinsonian and cerebellar signs

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ABSTRACT

Apart from intention tremor essential tremor (ET) patients may display other cerebellar signs, like dysmetria or tandem gait disturbances as well as parkinsonian signs like resting tremor, cogwheel sign, subtle bradykinesia. Previous reports claimed the occurrence of the eye movement abnormalities characteristic for dysfunction of cerebellar dorsal vermis in ET patients with concomitant cerebellar signs. There are no previous reports evaluating the eye movement abnormalities in ET patients with concomitant parkinsonian signs.

The objective of this study was to determine the relationship between the occurrence of parkinsonian and cerebellar signs and the oculomotor abnormalities in ET patients.

Method: Fifty ET patients including 6 (12.0%) patients with concomitant parkinsonian signs (ET-P), 20 (40.0%) patients with cerebellar signs (ET-C), 7 (14.0%) with mixed parkinsonian and cerebellar signs (ET-M), 17 (34.0%) patients with the only tremor (ET-T) together with 42 healthy controls were included to the study. Reflexive, pace-induced and cued saccades were recorded using Saccadometer Advanced. Smooth pursuit and fixation were tested using EOG.

Results: Latency of pace-induced saccades was significantly longer in ET-C and ET-M patients compared to ET-T and ET-P patients. Latency of cued saccades was significantly longer in ET-M patients compared to ET-T. There were no significant differences of the eye movement parameters between ET-P patients compared to ET-T patients.

Conclusion: In ET patient with concomitant cerebellar signs prolonged volitional saccades latency was detected. There are no particular differences in the eye movements in ET patients with concomitant parkinsonian signs compared to ET patients without concomitant signs.

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1. Introduction

Until very recently, essential tremor (ET) has been regarded as a monosymptomatic entity characterized by action tremor involving mainly hands and forearms, less commonly head, voice, jaw, trunk and lower extremities. However, clinical observations of recent years showed that ET patients may display the other motor (parkinsonian, cerebellar, oculomotor) as well as non-motor (personality disturbances, depression, fear, fatigue, sleep disturbances, cognitive deficits, pain, hearing and olfaction loss) symptoms and signs [1]. Parkinsonian signs including resting tremor [2–5], subtle bradykinesia [6], slight arm rigidity in the form of cogwheel sign [7], decreased arm swing or hypomimia [8] occur in elderly patients. Likewise, cerebellar signs, so as intention tremor [9], dysidiadochokinesia and impaired tandem gait [10–14] usually appear in advanced stage of ET. The presence of parkinsonian or cerebellar signs might cause misdiagnosis of even 20–50% of ET cases mainly as parkinsonism or cerebellar syndrome [15–17].

Deuschl et al. [18] distinguished the cerebellar dysfunction in ET patients from that of patients with other cerebellar degeneration by the absence of the eye movement disturbances. However, Helmchen et al. [19] founded eye movement changes originated from cerebellar dorsal vermis dysfunction like impaired smooth pursuit initiation and pathological suppression of vestibulo-ocular reflex by heat tilt in ET patients with dominant intention tremor. Gitchel et al. [20] assessed eye movements in 60 ET patients regardless of the co-occurrence of concomitant signs and found abnormalities of dynamic parameters in reflexive saccades including prolonged latency and decrease velocity and fixation break by increase number of square wave jerks intrusions. Our previous study of 50 ET patients indicated the presence of the cerebellar oculomotor abnormalities including reflexive saccades dysmetria and deficit of smooth pursuit and no abnormalities of pace-induced saccades, cued saccades and fixation [21]. To the best of our knowledge there are no previous reports evaluating the eye movement abnormalities in ET patients with concomitant parkinsonian signs.

The aim of this study was to assess the relation between the occurrence of parkinsonian and cerebellar signs and the oculomotor abnormalities in ET patients.

2. Methods

The participation in the study was proposed to all patients diagnosed as ET visited the Movement Disorders Clinic, Department of Neurology, University Hospital in Cracow, Poland between January 2008 and June 2010. The diagnosis of ET was made according to the National Institute of Health Collaborative Genetic Criteria (1996) [22]. Exclusion criteria were: restriction of the eyes motility, scotomy, severe refraction abnormalities, red or green color blindness, other diseases of nervous system or muscles which cause oculomotor abnormalities, taking drugs which influence the eye movements except levodopa, propranolol and prymidon, alcohol or drugs abuse, past intoxication by drugs, carbon

monoxide or other chemical agent, schizophrenia or other sever psychiatric disease, symptomatic hypo- or hyperthyroidism, autoimmune disease, malignancy, severe cardiac, renal, hepatic or pulmonary insufficiency, and contraindication for MRI. The presence of exclusion criteria was verified based on interview and neurological examination, laboratory tests including TSH and ceruloplasmine blood level, ophthalmic examination, brain MRI and other examinations as needed. In order to exclude Parkinson disease each patient underwent levodopa challenge.

The control group, matched by age (± 3 years) and gender, was recruited from patients' spouses and acquaintances. All control subjects fulfilled qualification criteria to the study.

Before the beginning of the research procedures each participant signed written consent for participation in the study. The study was approved by the Jagiellonian University Bioethics Committee. All research procedures were performed in compliance with the principles in the Declaration of Helsinki.

Patients with ET were interviewed about the age of disease onset, character of symptoms and disease course. Patients and controls were asked about concomitant medical history, current medication, stimulants, contact with toxic substances and family history. Each participant underwent neurological examination extended by the Mini Mental State Examination and evaluation of depression symptoms in the Beck Depression Inventory (BDI). The severity of tremor was assessed using the Clinical Rating Scale for Tremor (CRST) [23].

For each subject we assessed reflexive saccades, two types of volitional saccades including pace-induced saccades and cued saccades, smooth pursuit and fixation. The methodology of assessment of the eye movements was described in our previous publication [21].

2.1. Statistic methods

The statistical analysis was performed using STATISTICA software (version 9.0 for Windows 7.0, StatSoft. Inc., PL). Numeric variables were present as mean \pm standard deviation (SD). Normal population distribution was verified by the Kolmogorov–Smirnov test. Differences between categorical variables were analyzed by Pearson χ^2 test or, in case of small sample size, by Fisher's test and between parametric variables by Kruskal–Wallis one-way analysis of variance for more than two groups. In the post hoc analysis Dunn's test was applied. A p value < 0.05 was considered significant.

3. Results

Fifty eligible ET patients (mean age: 59.2 ± 21.7 years, 26 men and 24 women) and 42 healthy volunteers (mean age: 60.6 ± 19.0 years, 17 men and 25 women) agreed for participation in the study. There were no significant differences in age and gender between patients with ET and controls.

The group of ET patient was divided into four subgroups according to the presence of parkinsonian and cerebellar signs. There were 17 (34%) patients with the only tremor (ET-T), 6 (12%) with parkinsonian signs (ET-P), 20 (40%) with cerebellar signs (ET-C) and 7 (14%) with mixed parkinsonian and

Table 1 – The results of the eye movement assessment in patients with ET with relation to the presence of concomitant parkinsonian and cerebellar signs.

Type of the eye movement	Parameter	ET-T	ET-P	ET-C	ET-M	P	Post hoc
Reflexive saccades	Latency (ms)	225.7 ± 90.4	283.7 ± 76.6	272.1 ± 97.7	298.86 ± 47.0	Ns.	
	Amplitude (deg)	19.0 ± 3.3	19.0 ± 2.8	17.6 ± 4.5	18.4 ± 1.8	Ns.	
	Hypometria (%)	6 (35.3%)	3 (50.0%)	8 (40.0%)	4 (57.1%)	Ns.***	
	Dysmetria (%)	3 (17.6%)	1 (16.7%)	4 (20.0%)	1 (14.3%)	Ns.***	
	Velocity (deg/s)	529.9 ± 62.4	520.2 ± 93.4	472.2 ± 117.2	488.1 ± 51.5	Ns.	
Pace-induced saccades	Number	50.7 ± 14.0	45.5 ± 4.3	44.0 ± 11.6	39.7 ± 10.5	Ns.	
	Latency (ms)	593.5 ± 132.0	633.2 ± 66.0	821.7 ± 123.2	998.4 ± 123.2	0.000 ^a	ET-T vs. ET-M: 0.001 ET-T vs. ET-M: 0.001 ET-P vs. ET-C: 0.031 ET-P vs. ET-M: 0.003
	Amplitude (deg)	19.6 ± 4.1	18.8 ± 2.4	20.4 ± 5.1	17.2 ± 4.0	Ns.	
	Hypometria (%)	1 (5.9%)	0	0	0	Ns.***	
	Velocity (deg/s)	528.3 ± 118.5	515.2 ± 38.4	513.5 ± 151.4	450.1 ± 109.6	Ns.	
Cued saccades	Error rate (%)	24.1 ± 24.2	26.4 ± 14.2	31.6 ± 15.2	37.0 ± 18.7	Ns.	
	Latency (ms)	453.3 ± 83.9	512.3 ± 139.8	544.0 ± 126.7	712.8 ± 126.4	0.009 ^a	ET-T vs. ET-M: 0.003
Smooth pursuit	SPG (%)	80.8 ± 7.9	69.8 ± 16.8	71.8 ± 10.1	72.0 ± 16.0	Ns.	
OKN	OKNG (%)	16.7 ± 1.4	11.5 ± 15.5	9.2 ± 4.8	13.5 ± 6.8	Ns.	
Saccadic intrusions	No. of patients (%)	0	0	0	2/6 (33.3%)	Ns.***	
ET-T, ET patients with the only tremor; ET-P, ET patients with parkinsonian signs; ET-C, ET patients with cerebellar signs; ET-M, ET patients with mixed parkinsonian and cerebellar signs.							
^a Kruskal-Wallis one-way analysis of variance, post hoc analysis by Dunn's test.							
*** Pearson χ^2 test.							

cerebellar signs (ET-M). There were no significant differences of age (respectively: 48.1 ± 23.0, 64.8 ± 11.0, 64.5 ± 21.1, 65.0 ± 21.1 years) and age at disease onset (36.9 ± 21.5, 39.8 ± 24.7, 42.7 ± 21.6, 40.8 ± 20.4 years) between ET subgroups. There were significant differences of disease duration between subgroups of ET patients (respectively: 16.1 ± 31.0 years, 29.4 ± 16.7 years, 21.1 ± 13.0 years, 25.5 ± 9.7 years; $p = 0.002$). Disease duration was significantly shorter in ET-T patients compared with ET-P ($p = 0.018$), ET-C ($p = 0.009$) and ET-M ($p = 0.008$). Similar significant differences were found for the disease severity assessed by CRST (20.7 ± 11.9, 32.7 ± 8.5, 33.3 ± 12.5, 43.1 ± 18.0; $p = 0.002$). Tremor severity was significantly lower in ET-T than ET-C ($p = 0.005$) and ET-M patients ($p = 0.000$). Among ET-P patients there were 3 (50.0%) ones with resting tremor, bradykinesia and cogwheel sign, 1 (16.7%) with resting tremor and cogwheel sign, and 1 (16.7%) patient with bradykinesia. Among ET-C patients there were 10 (50.0%) patients with intention tremor, 3 (15.0%) ones with dysidiadochokinesia, 3 (15.0%) ones with intention tremor and dysidiadochokinesia, 2 (10.0%) ones with intention tremor and tandem gait disturbances and 2 (10.0%) patients with intention tremor, dysidiadochokinesia and tandem gait disturbances. In ET-M group there were 5 (83.3%) patients with bradykinesia and intention tremor and in 1 (16.7%) patient resting tremor, bradykinesia, intention tremor and tandem gait disturbances.

In the analysis of volitional saccades parameters significant prolongation of pace-induced saccades latency in patients with cerebellar signs (ET-C and ET-M) compared with the other subgroups (ET-T, ET-P) and prolongation of cued saccades latencies in ET-M compared with ET-T patients were found. There were no significant differences of reflexive saccades

parameters, other than latency volitional saccades parameters and smooth pursuit parameters between ET-T, ET-P, ET-C and ET-M patients (Table 1).

4. Discussion

The study revealed the occurrence of prolonged latency of volitional saccades in the subgroup of ET patients with concomitant cerebellar signs. On the contrary, in the subgroup of ET patients with concomitant parkinsonian signs eye movement abnormalities, which might be distinguishing, were not found.

The study showed that the latency of pace-induced saccades and cued saccades is prolonged in ET patients with concomitant cerebellar signs. It was an unexpected findings, because the pathophysiology of those abnormalities is not considered as characteristic feature for dysfunction of cerebellum, brainstem or their connections, which are supposed to be the site of ET pathology [24,25]. Impaired initiation of volitional saccades was described in the other neurodegenerative disease, like PD and Huntington disease (HD), in which the pathological process involves higher brain regions including cortical regions, basal ganglia and fronto-subcortical connections. The execution of pace-induced saccades, meant saccades made alternately between two stationary targets, depends primarily on the basal ganglia [28]. In PD and HD pace-induced saccades are characterized by prolonged latency and decreased amplitude [26,27]. The performance of cued saccades is controlled by dorso-lateral prefrontal cortex [28]. In HD [27] cued saccades are characterized by prolonged

latency and increased number of incorrect saccades. The results of our study suggested that in ET, like in HD [27,29,30] and PD [31–33], the dysfunction of frontal regions or fronto-subcortical connections is also present. Other oculomotor abnormalities connected with dysfunction of that structures like decrease number of pace-induced saccades and increase rate of incorrect cued saccades were not found in any subgroups of ET patients, which suggest that the degree of damage is mild.

The presence of frontal dysfunction in ET was confirmed by neuropsychological and functional imaging studies [34–36].

Neuropsychological studies have been shown that cognitive functions supported by prefrontal cortex and fronto-cerebellar network are mildly impaired in ET patients. The cognitive dysfunction in ET is characterized by subclinical deficits of executive function, attention, working memory, visuo-spatial orientation and verbal fluency [36–43].

Sahin et al. [34] in the study of young ET patients and healthy controls using single photon emission computed tomography revealed significant negative correlation between decrease in regional blood flow in frontal regions and severity of tremor as well, as the results of some neuropsychological tests assessing frontal functions. The positive correlation between severity of tremor and the results of tests assessing executive functions was also found. These results suggest the presence of pathology, which cause together tremor and cognitive dysfunction involving fronto-cerebellar circuits in ET. Ceresa et al. [35] using functional magnetic imaging studies (fMRI) revealed increased activity in ET patient compared to controls in dorso-lateral prefrontal cortex (DLPFC) and inferior parietal lobe (IPL) during performing test involving executive functions. Since no differences in neuropsychological test were found between ET patients and controls, the results of the study suggest the presence compensation mechanism of executive frontal dysfunction in ET. In the study of Passamonti et al., who used fMRI as well, the task of the participants was to perform test involving working memory [36]. The study showed the dysfunction of connections between structures supporting executive functions (DLPFC, thalamus, IPL) and some regions of the cerebellum in ET patients, who got minor score in neuropsychological tests. There is a need of studies assessing the relation between eye movement abnormalities and cognitive functions as well, as functional imaging examinations in ET patients.

The presence of mild parkinsonian signs was described in ET patients [2–8]. The eye movement parameters in the subgroup of ET patients with concomitant parkinsonian signs were not significantly different from that ones without concomitant signs. We did not find abnormalities of reflexive saccades nor pace-induced saccades in this group, which are characteristic for PD [31–33]. The etiology of parkinsonian signs accompanying ET has not been explained yet. Most of authors claim that they result from age-related loss of neurons in the substantia nigra and they are unresponsive to levodopa treatment [2–8]. Neuropathological studies and functional imaging studies did not confirmed the presence of features characteristic for PD. Louis et al. in the autopsies studies of 9 ET patients with rest tremor no Lewy bodies were found [5]. DaTScan studies did not reveal reduction of dopamine transporter density in ET patients with resting tremor

[44–46]. Only ultrasonography revealed hyperechogenic substantia nigra in 16% of ET, 90% of PD patients and only 9% of healthy controls [47].

The limitation of this study was small number of ET patients with concomitant parkinsonian signs. The results of this study particularly concerning the assessment of oculomotor abnormalities in ET patients with concomitant parkinsonian signs.

Findings from this study support the hypothesis of fronto-cerebellar circuits involvement in ET.

Conflict of interest

None declared.

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Ethics

The work described in this article has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans; Uniform Requirements for manuscripts submitted to Biomedical journals.

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